Summary

An attempt has been made to determine what association, if any, exists between chronic dyspepsia and the presence of gall-stones, determined radiologically in women aged 50–70 years.

The survey was conducted in a general practice to avoid the selection inevitable in a hospital population.

The women were interviewed before being *x*-rayed, so that their histories were not biased by any knowledge of whether gall-stones were present or not.

A history of dyspepsia was obtained from 12 (50%) out of 24 subjects with gall-bladder disease. Of those with normal cholecystograms 63 (53%) out of 118 had similar symptoms.

The dyspepsia suffered by those with gall-stones was not distinguishable from that experienced by those with normal gall-bladders.

It is concluded that among women aged between 50 and 70 the occurrence of chronic dyspepsia and gall-bladder disease is coincidental. These symptoms cannot assist in diagnosis of gall-bladder disease and should not influence its treatment.

I am grateful to Dr. E. B. French for suggesting this inquiry and for helpful criticism; to Dr. R. C. McNair for enlisting the co-operation of his patients; to Mr. S. A. Sklaroff for advice on the collection and interpretation of data; and to Dr. W. N. Thomson, Dr. J. T. Wright, and Dr. D. H. Cummack for reports on the cholecystograms.

REFERENCES

Akerlund, A. (1938). *Acta radiol. (Stockh.)*, **19**, 23.
Alvarez, W. C. (1943). *Nervousness, Indigestion, and Pain*, p. 49. Heinemann, London.
Barker, L. F. (1920). *J. Amer. med. Ass.*, **75**, 1105.
Bockus, H., and Dozzi, D. L. (1946). In H. L. Bockus's *Gastroenterology*, vol. 3, p. 596. Saunders, Philadelphia.
Colp, R., Doubilet, H., and Gerber, I. E. (1935). *Ann. Surg.*, **102**, 202.
—— Gerber, I. E., and Doubilet, H. (1936). Ibid., **103**, 67.
Gordon, I. R. S. (1953). *Quart. J. Med.*, **22**, 261.
Ivy, A. C., Grossman, M. J., and Bachrach, W. H. (1950). *Peptic Ulcer*, p. 819. Churchill, London.
Kehr, H. (1901). *Introduction to the Differential Diagnosis of the Separate Forms of Gallstone Disease*, translated by W. W. Seymour. Blakiston, London.
Mayo, W. J. (1911). *J. Amer. med. Ass.*, **56**, 1021.
Moynihan, B. G. A. (1908). *Gallstones and their Surgical Treatment*, p. 147. Saunders, Philadelphia.
Rivers, A. B., and Ferreira, A. E. M. (1938). *J. Amer. med. Ass.*, **110**, 2132.
Robertson, H. E. (1945). *Gastroenterology*, **5**, 345.
Truesdell, E. D. (1944). *Ann. Surg.*, **119**, 232.

INCIDENCE OF HYPOMAGNESAEMIA IN INTESTINAL MALABSORPTION

BY

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Electrolyte deficiencies are a common complication of intestinal malabsorption. However, although subnormal serum levels of sodium, potassium, and calcium frequently occur, magnesium deficiency has been described only on rare occasions until recently. Single cases with subnormal serum magnesium levels have been reported by several groups of workers (Card and Marks, 1958; Fletcher, Henly, Sammons, and Squire, 1960; Hanna, Harrison, MacIntyre, and Fraser, 1960; Vallee, Wacker, and Ulmer, 1960; MacIntyre, Hanna, Booth, and Read, 1961; Goldman, Van Fossan, and Baird, 1962), but the incidence of magnesium deficiency in patients with intestinal malabsorption and its clinical significance have not been studied hitherto.

In this paper we report the serum magnesium concentrations in 42 patients suffering from intestinal malabsorption due to a variety of causes. The incidence of subnormal serum magnesium levels and their relation to the concentrations of other electrolytes and to faecal fat excretion are described. Balance studies and responses to treatment are also given.

Materials and Methods

Chemical Estimations.—Magnesium was measured by the method described by Alcock, MacIntyre, and Radde (1960), calcium by the method of MacIntyre (1961), and sodium and potassium as described by King and Wootton (1956). Faecal fat was estimated by the method of Van der Kamer (1958).

Balance Studies.—Balance studies were carried out in a metabolic unit and were usually made during successive three-day periods after an initial equilibration period of five days. Chromium sesquioxide in oral doses of 0.5 g. thrice daily was used as a marker (Whitby and Lang, 1960). The chromium content of stools was estimated by flame spectrophotometer after extraction of the chromium into 4-methyl-2-pentanone (H. Anstell and J. Daley, unpublished observations).

Patients Studied.—Observations were made on 24 patients suffering from idiopathic steatorrhoea, on seven with steatorrhoea following partial gastrectomy, and on seven who had undergone partial resection of the small intestine or who had intestinal blind loops. There were also four other patients with steatorrhoea associated with intestinal lymphectasia (1), Whipple's disease (1), or chronic biliary obstruction (2).

Serum Magnesium Levels and Concentrations of Ca^{++}, Na^{+}, and K^{+}

The results of the serum magnesium estimations together with the concentrations of calcium, sodium, and potassium are shown in Fig. 1.

Idiopathic Steatorrhoea.—Ten of the 24 patients with idiopathic steatorrhoea had serum magnesium levels of less than 1.5 mEq/l., the lower limit of the normal range. In only two of these patients was the level lower than 1 mEq/l. Both of these latter patients had levels of 0.7 mEq/l. and they had strikingly low serum calcium levels in addition (3.4 and 3.9 mEq/l.). The serum calcium levels were also low in five of the other eight patients whose serum magnesium levels were subnormal; one of these, whose serum magnesium level was 1.3 mEq/l., had a serum calcium of only 2.6 mEq/l. However, subnormal serum calcium levels were also recorded in four of the remaining

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14 patients whose serum magnesium level was 1.5 mEq/l. or more. Serum sodium levels were normal or only slightly subnormal in all the patients, and no patient had a serum potassium level of less than 3 mEq/l., although five had levels of serum potassium of less than 4 mEq/l.

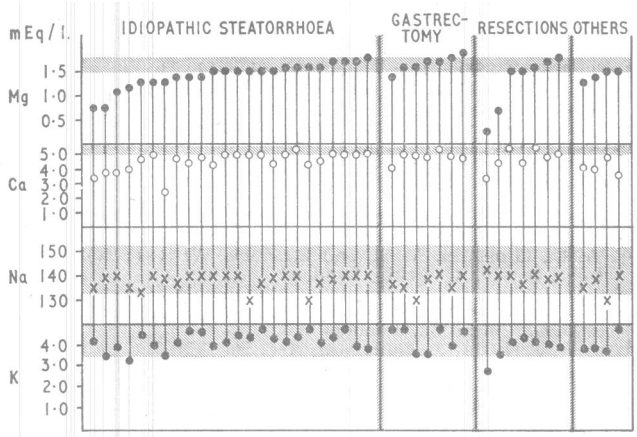

FIG. 1.—Serum Mg++, Ca++, Na+, and K+ in 42 patients suffering from intestinal malabsorption. The hatched areas indicate the normal ranges.

Partial Gastrectomy.—One of the seven patients had a slightly subnormal serum magnesium level (1.4 mEq/l.), and in this patient the serum calcium was also low (4.1 mEq/l.). Slight reductions of serum calcium occurred in two patients with a normal serum magnesium.

Resections and Blind Loops.—Two patients were hypomagnesaemic. One was extremely magnesium-deficient; the serum level was only 0.3 mEq/l. This patient's serum calcium and serum potassium levels were also very low (3.5 and 2.8 mEq/l. respectively). The second patient had a serum magnesium of 0.7 mEq/l.; but in this case, although the serum calcium was reduced to 4.3 mEq/l., the serum potassium was normal.

Other Patients.—Two patients in this group (one with intestinal lymphectasia, the other suffering from Whipple's disease) had slightly subnormal serum magnesium levels: in both patients the serum calcium levels were also low. Serum magnesium was normal in the other two patients, who had chronic biliary obstruction, although the serum calcium level was markedly reduced in the second (3.8 mEq/l.).

Magnesium Levels in Muscle and Bone

The concentration of magnesium in bone and muscle was measured in two patients from whom both muscle and bone biopsies were taken at the time when their serum magnesium levels were subnormal. The results are given in Table I. Bone magnesium content is probably best expressed by the Mg/Ca ratio, which is unaffected by differences in total bone mineral content.

TABLE I.—*Muscle and Bone Mg++ in Two Patients with Hypomagnesaemia*

Case No.	Serum Mg++ (mEq/l.)	Muscle Mg++ (mEq/kg. Dry Fat-free Solid)	Bone Mg++ (mEq/kg. Dry Fat-free Solid)	Bone Ca++ (Eq/kg. Dry Fat-free Solid)	Bone Mg/Ca Ratio
1*	0·7	47	191	12·3	0·0155
4	0·3	62	169	10·9	0·0155
Normals*	1·5–1·8	71 (63–78)	226 (212, 233, 233)	12·1 (11·6, 11·6, 13·2)	0·0187 (0·0177, 0·0182, 0·0201)

* Results for normals and Case 1 are taken from MacIntyre *et al.* (1961).

In the first patient, who suffered from idiopathic steatorrhoea and whose serum magnesium was 0.7 mEq/l., there was a striking reduction in muscle magnesium although the Mg/Ca ratio of bone was less markedly reduced (MacIntyre *et al.*, 1961). There was also a moderate reduction in the bone Mg/Ca ratio in the second patient (who had undergone extensive resection of the distal small intestine), but the muscle magnesium was only slightly reduced. The bone magnesium was therefore largely intact in both patients despite the marked degree of hypomagnesaemia, indicating that in adult man most of the bone magnesium is not readily available.

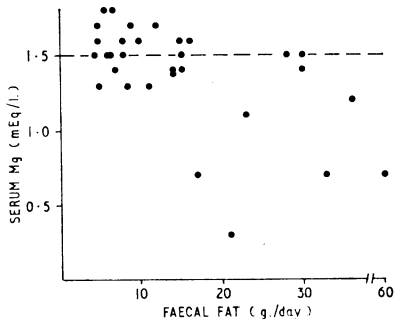

FIG. 2.—Relationship of serum Mg++ and faecal fat excretion.

Serum Magnesium Levels and Faecal Fat Excretion

The relation between the serum magnesium level and the faecal fat excretion is shown in Fig. 2. It can be seen that in general the lowest serum magnesium levels were found in patients whose steatorrhoea was most pronounced.

Magnesium Balances

Magnesium balances were carried out in the five patients with the lowest serum magnesium levels. The results of these balance studies are given in Table II.

Two of the three patients with idiopathic steatorrhoea (Cases 1 and 2, Table II) were in negative magnesium

TABLE II.—*Magnesium Balances in Five Patients with Hypomagnesaemia*

Case No.	Diagnosis	Serum Mg++ (mEq/l.)	Mg++ Intake (mEq/day)	Urinary Mg++ (mEq/day)	Faecal Mg++ (mEq/day)	Balance (mEq/day)	Faecal Fat (g./day)	Remarks
1	Idiopathic steatorrhoea	0·7	13	0·2	14·2	−1·4	27·5	On low Ca++ diet (18 mEq/day)
		0·9	13	0·9	19·4	−7·3	27·5	,, high Ca++ diet (103 mEq/day)
		1·5	113	11·9	86·5	+14·6	—	,, ,, Mg++ intake
2	,,	0·7	20	0·1	40·5	−20·4	61·5	Ultimately died from malignant lymphoma of small intestine
			20	0·1	43·0	−23·0	90·0	
3	,,	1·1	12	2·4	9·6	0	24·0	Serum Mg++ rose to normal spontaneously (Fig. 3)
4	Resection of distal small intestine	0·3	14·0	0·2	7·2	+6·6	8·4	On low-fat diet (32 g. daily)
			12·0	0·0	9·1	+2·9	13·0	After calciferol 100,000 units daily for 5 days
		1·5	14·0	1·9	24·0	−11·9	19·0	On high-fat diet (138 g. daily)
			14·0	0·8	20·0	−6·8	21·0	,, ,, ,, ,,
5	Resection of terminal 4 ft. (1·2 m.) of ileum—recurrence of Crohn's disease in ileum and colon	0·7	18·0	0·3	20·0	−2·3	16·5	,, low-fat diet (32 g. daily)
			16·0	0·2	21·0	−5·2	17·9	,, ,, ,, ,,

balance when taking a moderately low intake (13 and 20 mEq/day respectively). This negative magnesium balance was aggravated when a high calcium intake was given in Case 1, but a positive magnesium balance was achieved when the magnesium intake was increased to 113 mEq/day. The third patient (Case 3) was in equilibrium so far as magnesium was concerned when the studies were made.

The fourth patient (Case 4) had severe magnesium deficiency associated with an extensive resection of the distal small intestine. Before admission to hospital she had been treated with a high-fat diet. On a low-fat diet (32 g./day), however, she was in positive magnesium balance. Calciferol (100,000 units daily for five days) was then given, as the serum calcium was very low (3.6 mEq/l.). This raised the serum calcium to normal, but the serum magnesium remained low and the magnesium balance revealed that less magnesium was retained than during the first balance. Subsequently, a high-fat diet was again given (138 g. daily); this resulted in an exaggeration of the steatorrhoea, and a negative magnesium balance was induced.

The fifth patient (Case 5) had undergone resection of the distal small intestine for Crohn's disease, but the disease had recurred in both ileum and colon. This patient remained in negative magnesium balance despite a low-fat diet (32 g. daily).

Responses to Treatment

Patients who had serum magnesium concentrations of between 1 and 1.5 mEq/l. required no magnesium supplements. In these patients the serum magnesium usually rose to normal levels when their underlying disease was treated. An illustrative response in a patient with idiopathic steatorrhoea and anaemia (Case 3), treated with folic acid, is shown in Fig. 3.

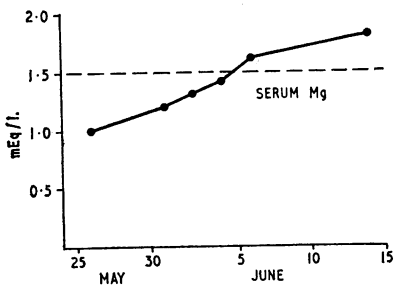

FIG. 3.—Spontaneous return of serum Mg++ to normal in a patient with idiopathic steatorrhoea treated with folic acid. The interrupted line indicates the lower limit of the normal range (Case 3, Table II).

Serum magnesium concentrations of less than 1 mEq/l. were of greater significance, and in idiopathic steatorrhoea seemed to parallel clinical severity. Both the patients whose serum magnesium levels were 0.7 mEq/l. were elderly; they were severely ill and both subsequently died of their disease. The response to treatment in the first patient (Case 1) is shown in Fig. 4. Oral magnesium supplements (magnesium chloride 100 mEq daily in divided dosage) induced a positive magnesium balance (Table II) and restored the serum magnesium to normal. The serum level remained normal during a remission of the disease induced by a gluten-free diet. When there was a subsequent relapse, which led ultimately to the death of the patient, the serum magnesium again fell and remained low despite oral magnesium supplements. Similarly, in Case 2 the serum magnesium rose with oral magnesium supplements but fell again before the patient's death, which was due to an associated malignant condition of the small intestine.

The remaining two patients, who had severe hypomagnesaemia associated with resection of the distal small intestine, had serum magnesium levels of 0.3 and 0.7 mEq/l. respectively. The first (Case 4) had undergone extensive resection of the distal small intestine but had no active intestinal disease. No magnesium supplements were given, but on a high-protein low-fat diet the serum magnesium

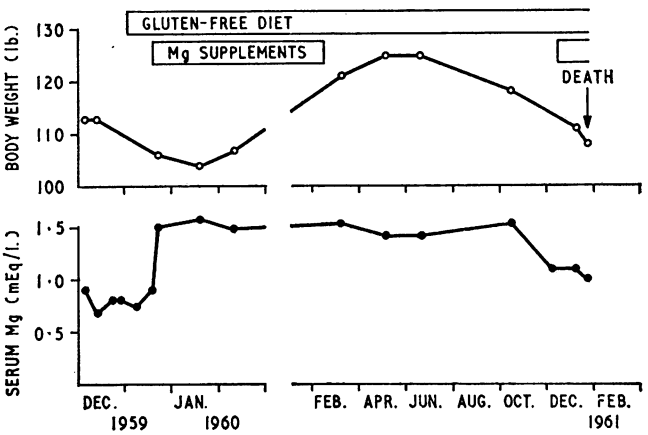

FIG. 4.—Serum Mg++ during gluten-induced remission and subsequent relapse in an elderly patient with idiopathic steatorrhoea who ultimately died from his disease (Case 1, Table II).

rose to normal levels (Fig. 5). The balance studies given in Table II reveal the reason for this response. On the low-fat diet there was only slight steatorrhoea and the patient was in positive magnesium balance. A high-fat diet, however, resulted in an increased faecal fat excretion; a negative magnesium balance was induced and the serum magnesium fell (Fig. 5).

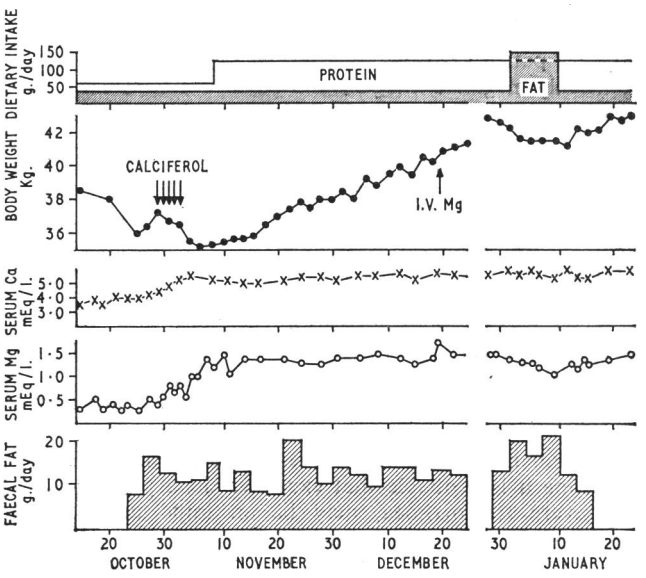

FIG. 5.—Body weight, serum Mg++ and Ca++, and faecal fat excretion during treatment first with a low-fat diet and then with a high-fat diet, in a patient with severe hypomagnesaemia associated with an extensive resection of the distal small intestine (Case 4, Table II).

However, treatment with a low-fat diet in Case 5 was ineffective, for he remained in negative magnesium balance (Table II) and the serum magnesium remained subnormal. This patient had active Crohn's disease affecting both small and large intestine, and this may have contributed to intestinal magnesium loss despite control of the steatorrhoea. His serum magnesium subsequently rose to normal when he was treated with prednisone.

Clinical Features of Magnesium Deficiency

No diagnostic clinical features were noted in the patients whose serum magnesium concentration ranged from 1 to 1.5 mEq/l.

Patients who had lower serum magnesium levels (<1 mEq/l.) invariably had spontaneous tetany, but all these patients also had subnormal serum calcium levels. It seems unlikely that their tetany was due to magnesium deficiency, for when their serum calcium levels were restored to normal the tetany invariably disappeared even when the serum magnesium level remained as low as before. Chvostek's and Trousseau's signs were also negative, provided that the serum calcium was normal, although the serum magnesium was less than 0.5 mEq/l. in one patient (Case 4, Table II, Fig. 5).

Discussion

The results given in this paper show that subnormal serum magnesium levels commonly occur in patients with idiopathic steatorrhoea or when steatorrhoea follows resection of the distal small intestine. If 1.5 mEq/l. is taken as the lower limit of the normal range (Alcock *et al.*, 1960), hypomagnesaemia was in fact more commonly encountered than hypocalcaemia in these patients. Whether these levels invariably indicate tissue depletion of magnesium is uncertain, but in one patient the low serum magnesium levels were shown to be associated with a marked reduction in the muscle magnesium, although bone magnesium remained largely intact (Table I).

Magnesium deficiency in these patients was clearly due to intestinal magnesium loss (Table II), and, as might be expected, there was a rough correlation between the serum magnesium level and the degree of steatorrhoea (Fig. 2). In two patients with idiopathic steatorrhoea there was a markedly negative magnesium balance unless large oral magnesium supplements were given. In one of these patients (Case 1) a high oral calcium intake exaggerated the negative balance. This finding is in keeping with the demonstration of a common intestinal transport mechanism for calcium and magnesium (Schachter and Rosen, 1959; Alcock and MacIntyre, 1960, 1962) and illustrates why severe magnesium deficiency may occasionally be caused by overzealous treatment of such patients with calcium (Hanna *et al.*, 1960). The third patient with idiopathic steatorrhoea in whom balances were carried out (Case 3) was just in equilibrium; it is interesting that the serum magnesium in this patient rose spontaneously when treatment with folic acid was given (Fig. 3).

In patients with extensive resection of the distal small intestine it is probable that excessive dietary fat, resulting in severe steatorrhoea, may be an important cause of magnesium deficiency. This is illustrated by the results in one patient (Case 4, Table II), whose serum magnesium level on admission to hospital was only 0.3 mEq/l.—a very severe degree of hypomagnesaemia. Yet on a low-fat diet (32 g. daily) she was in positive magnesium balance and her serum magnesium rose to normal levels without any magnesium supplements being given (Fig. 5). A high-fat diet, however, caused an exacerbation of steatorrhoea and induced both a negative magnesium balance (Table II) and a reduction in the serum level (Fig. 5). Such responses may be expected if the intestine has merely been resected, but a low-fat diet may be ineffective if the bowel is actively involved by disease, as in the other patient who had hypomagnesaemia associated with a distal intestinal resection (Case 5). This patient, who had active Crohn's disease involving the small and the large intestine, remained in negative magnesium balance despite a low-fat diet, presumably because of loss of magnesium in intestinal secretions from the diseased bowel. This conclusion is supported by the observation that the serum magnesium rose to normal after a remission was induced by prednisone.

Magnesium deficiency in these patients seemed in general to parallel clinical severity; as already stated, the serum level in many patients rose to normal when the underlying disease was correctly treated (Figs. 3 and 5). Spontaneous tetany, or positive Chvostek's and Trousseau's signs, was found only when the serum calcium levels were also low and invariably disappeared when the serum calcium returned to normal, even when the serum magnesium remained as low as before. Mental changes and even convulsions have been described in severe magnesium deficiency (Hanna *et al.*, 1960), but did not occur in the patients in this series. Magnesium deficiency, like potassium deficiency, rarely causes a specific clinical picture. Nevertheless, there are three reasons for giving magnesium supplements in marked hypomagnesaemia: (1) magnesium is essential to many enzyme systems in the body; (2) in experimental animals hypomagnesaemia uniformly causes renal damage and may therefore also cause renal changes in man; and (3) fatal epileptiform convulsions occasionally occur. In most instances 0.5 mEq/kg. body weight proves adequate, given as $MgCl_2$ in divided dosage. Occasionally larger amounts (up to 4 mEq/day) may be necessary.

Summary

Subnormal serum magnesium levels were found in 15 out of 42 patients suffering from intestinal malabsorption. In most patients hypomagnesaemia was not associated with any specific clinical signs. Patients with levels of less than 1 mEq/l. invariably also had hypocalcaemia and tetany, but their tetany was relieved when their serum calcium levels were restored to normal, although the serum magnesium might remain as low as before. Magnesium supplements should be given when the plasma magnesium is below 1 mEq/l.

The cause of hypomagnesaemia in these patients was a negative magnesium balance due to intestinal loss of magnesium. Factors influencing magnesium balance are described.

In two patients with hypomagnesaemia the low serum magnesium levels were found to be associated with a moderate reduction of the Mg/Ca ratio in bone; in one there was also a marked reduction in muscle magnesium.

References

Alcock, N., and MacIntyre, I. (1960). *Biochem. J.*, **76**, 19P.
—— —— (1962). *Clin. Sci.*, **22**, 185.
—— —— and Radde, I. (1960). *J. clin. Path.*, **13**, 506.
Card, W. I., and Marks, I. N. (1958). In *Ciba Foundation Colloquia on Ageing*, **4**, 301. Churchill, London.
Fletcher, R. F., Henly, A. A., Sammons, H. G., and Squire, J. R. (1960). *Lancet*, **1**, 522.
Goldman, A. S., Van Fossan, D. D., and Baird, E. E. (1962). *Pediatrics*, **29**, 948.
Hanna, S., Harrison, M., MacIntyre, I., and Fraser, R. (1960). *Lancet*, **2**, 172.
King, E. J., and Wootton, I. D. P. (1956). *Micro-Analysis in Medical Biochemistry*, 3rd ed. Churchill, London.
MacIntyre, I. (1961). *Advanc. clin. Chem.*, **4**, 1.
—— Hanna, S., Booth, C. C., and Read, A. E. (1961). *Clin. Sci.*, **20**, 297.
Schachter, D., and Rosen, S. M. (1959). *Amer. J. Physiol.*, **196**, 357.
Vallee, B. L., Wacker, W. E. C., and Ulmer, D. D. (1960). *New Engl. J. Med.*, **262**, 155.
Van der Kamer, J. H. (1958). *Standard Methods of Clinical Chemistry*, vol. II, edited by David Seligson. Academic Press, New York.
Whitby, L. G., and Lang, D. (1960). *J. clin. Invest.*, **39**, 854.